The Annals of Clinical and Analytical Medicine
Original Research

Conversion rate of prediabetes to diabetes in long-term followed patients

Salih Eker
Family Medicine, Sakarya University Research and Training Hospital, Adapazari, Sakarya, Turkey

Abstract

Aim: We aimed to determine the transition rate of the prediabetic state to Type 2 diabetes mellitus (T2DM) in the subjects for whom pharmaceutical intervention therapy was used. Method and Material: In this context, we analyzed the records of 39 prediabetic subjects who we had followed-up at approximately 3-month intervals for a mean duration of 8.77 years. The primary pharmaceutical agent used was metformin; acarbose and rosiglitazone were the other agents used. One subject used no pharmaceutical agent. Results: In the study we found a 43.6% transition rate to overt T2DM. 56.4 % of the subjects did not convert to DM and sustained their status as prediabetes. Discussion: This small but long-term study indicates the possibility that prediabetes can be at least partly prevented or T2DM onset can be delayed for years thorough pharmaceutical intervention. Furthermore, even if the prediabetic state is converted to DM, it can be managed with little intervention and we can maintain nearly the same glucose levels comparable to prediabetes.

Keywords

Prediabetes; Prevention; Metformin

DOI:10.4328/ACAM.5830 Received: 19.03.2018 Accepted: 10.04.2018 Published Online: 18.03.2019 Printed: 01.07.2019 Ann Clin Anal Med 2019;10(4): 421-5
Corresponding Author: Salih Eker, Family Medicine, Sakarya University Research and Training Hospital, 54100, Adapazari, Sakarya, Turkey.
GSM: +905557131383 E-Mail: salihekerdr@hotmail.com

Introduction

Type 2 diabetes mellitus (T2DM) has become a common and devastating disease worldwide. Preventing the disease from transitioning to its overt form is of utmost importance. Prediabetes has been explained by the presence of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). IGT is characterised by elevated postprandial glucose between 140-200 mg/dl and is identified by an oral glucose tolerance test (OGTT) whereby 2-hour glucose levels are measured after a 75 gr glucose load given in the fasting state. Both World Health Organization (WHO) and the American Diabetes Association (ADA) recognize 2-hour post challenge glucose levels of greater than or equal to 7.8 mmol L (140 mg/dl) and less than 11.1 mmol L (200 mg/dl) as indicating IGT [1,2]. IFG is characterized by elevated fasting glucose levels between 100 mg dl and 126 mg/dl (5.5 mmol L-7.0 mmol L) for ADA and 110 mg/dl-126 mg/dl (6.0 mmol L-7.0 mmol L) for WHO [1,2]. In-between these two boundaries exists a region of abnormal glucose control which is already characterized by concomitant insulin resistance and β-cell dysfunction but does not yet reach the criteria for T2DM [3]. Patients eventually diagnosed as T2DM spend an extended period in this region of impaired glucose regulation, sometimes for more than a decade, before progressing to outright T2DM [3].

Although National Institute for Health and Care Excellence (NICE) have recommended that HbA1c (A1c) levels of 6.0-6.5% can be used as an alternative to fasting or 2-hour glucose in the identification of prediabetes, evidence from United Kingdom (UK) and elsewhere suggest there is significant discordance in which individuals are identified with prediabetes through A1c levels versus traditional criteria [4,5].

There are two kinds of interventions to manage the prediabetes state. The; first is lifestyle intervention including managing obesity, physical activity, and diet, each of which has efficacy itself. The second is pharmaceutical intervention including in particular metformin, thiazolidinediones, alpha-glucosidase inhibitors and other agents. In this study we evaluated the second option. In this study, because there is still controversy over whether if the prediabetic state is a disease or not, we prefer the term ''subjects'' to describe the prediabetics.

Material and Method

The study was designed in a retrospective and cross-sectional manner and conducted after 2016 in Sakarya Research and Training Hospital in Turkey. The study protocol was approved by the ethics committee of Sakarya University on June 28, 2016, number 71522473/050.01.04/130. A1c was analyzed with PremierHb9210™ HbA1c analyzer. The instrument consists of an integrated HPLC system, a compact sample handler and the workstation with our Affinity™ control software. Serial Number: 100232, Kansas City, Trinity Biotech, USA. The data was designed and evaluated using the SPSS 20 program.

All the subjects were outpatients who were drug-naïve at the time of their first visit and diagnosed with diabetes or prediabetes. 39 patients were included into the study (30 (76.9%) female and 9 (23.1%) male) and subjects were selected from approximately 2500 files of patients who had been followed in the clinic for their diabetes or prediabetes. To diagnose the prediabetes state we used the internationaly adopted and afore mentioned WHO criteria [1]. Four of the subjects were diagnosed by oral glucose tolerance test (OGTT) while the other 35 were diagnosed according to the fasting glucose level criteria. All of the subjects had their own files and we followed these subjects at approximately 3-month intervals for a mean duration of 8.77 years. In particular, we used the pharmaceutical intervention measures to control the prediabetes state. The primary agent used was metformin, which has proved its efficacy and safety worldwide [6]. For subjects who converted to T2DM we increased the dose or added another agent to control glucose levels in an acceptable range. To identify conversion to T2DM, we used the aforementioned WHO criteria [1], which is fasting glucose level ≥ 126 mg/dl or A1c level ≥ 6.5%. During each visit, an A1c value was taken and saved in their files along with other parameters including biochemical ones (glucose, urea, creatinine, SGOT, SGPT, etc.), Body Mass Index (BMI) and systolic and diastolic tension values that were required to be logged for diabetes. Meanwhile, we also intended to manage confounding diseases including hypertension and dislipidemia, which are the most likely coexisting diseases with impaired glycemic status.

Exercise level was evaluated according to criteria of WHO recommendations on physical activity for health at the time of diagnosis [7] through asking the patient directly. WHO suggests 150 minutes of moderate-intensity exercise per week over daily routine activities. Because no subject could meet the criteria, between 120-150 minutes per week was accepted as the median level, while under 120 minutes per week was accepted as low level of exercise.

BMI of the subjects was calculated at every visit and recorded in their personal files. We used a BMI chart which takes into account the weight and height to calculate the value. Values taken at the baseline and at the last visit were taken into account in the study.

Blood tension values were measured at every visit through a manual manometer by experienced nurses and the values were recorded in the files. We used the baseline and the last value for statistical calculation.

For the majority of subjects, we commenced metformin as the therapy of first choice. We gave metformin 850 mg 1x1 for 18 (46.2%) subjects, metformin 850 mg 2x1 for 9 (23.1%) subjects, metformin 500 mg 2x1 for 8 (17.9%) subjects and metformin 1000 mg 2x1 for 1 (2.6%) subject. Acarbose [8] and rosiglitasone were other therapy options, and for one subject we gave no drug therapy. We gave acarbose 100 mg 3x1 for 2 (5.1%) patients and rosiglitazon 4 mg 1x1 for 1 (2.6%) subject (this subject could not tolerate metformin during the first stage and that is why we preferred rosiglitazone) but after withdrawal of rosiglitazone we did continue with pioglitazone 15 mg 1x1.

Results

30 (76.9%) of the 39 subjects enrolled were female and 9 (23.1%) were male. The mean age of the subjects at baseline was 50.15 and 58.92 at the end of the study. Mean years of follow-up was 8.77 (minimum 4, maximum 11). Mean fasting glucoses of the subjects were 110.05 at baseline and 112.82 at the end of the study, while mean A1c at baseline was 6.05% and 6.03% at the end of the study.

Exercise levels of the subjects were evaluated at the first visit and continued to be monitored until the last visit. The evaluation criteria are described under the methods and material section above. At the first visit, 15 (38.5%) subjects declared that they did not meet any acceptable level of exercise, 23 (59.0%) subjects declared low level of exercise and only 1 (2.6%) subject declared median level of exercise. At the last visit, 12 (30.8%) subjects declared that they could not meet any acceptable level

of exercise, 25 (64.1%) subjects declared low level of exercise and 2 (5.1%) subjects declared median level of exercise (p=0.394). Actually, exercise levels of the subjects throughout the follow-up period were smilar to those described above.

Mean BMI of the subjects calculated at baseline was 31.662, and it was 31.423 at last visit (p=0864). These results represent obesity at both times. Also, there were no significant difference between converted and unconverted subjects's BMIs both at the first and the last visits (Table 3).

Mean systolic and diastolic blood pressure of subjects at baseline were 127.69 and 75.13 respectively whereas they were 120.64 and 78.46 at the last visit (p=0.004 for systolic and p=0.026 for diastolic).

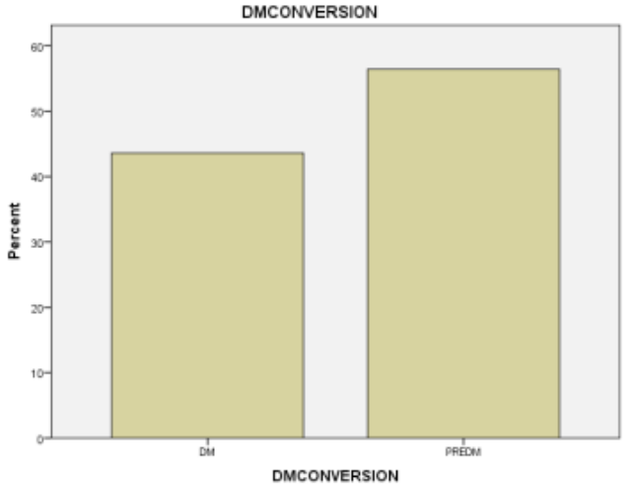
Smoking status of subjects stratified as 5 (12.8%) smokers, 24 (61.5%) nonsmokers, and 10 (25.6%) ex-smokers at the beginning of the study, and this status had not changed from first to last visit, maintaining the same profile (Table 1). No subjects were alcohol users, either at first or last visit.

Results of the of the study, which aimed to detect the conversion rate from prediabetes state to diabetes, were found as follows: 17 of 39 patients (43.6%) converted to DM, while 22 (56.4%) did not convert (Graphic 1) and managed to maintain their status as prediabetes (Table 1). In detail, 8 (44.4%) of 18 subjects started with metformin 850 mg 1x1 converted to DM while 10 (55.6%) did not, 5 (55.6%) of 9 subjects started with metformin 850 mg 2x1 converted to DM while 4 (44.4%) did not, 2 (28.6%) of 7 subjects started with metformin 500 mg 2x1 converted to DM while 5 (71.4%) did not, 1 subject started with metformin 1000 mg 2x1 maintained as prediabetes, 1 (50.0%) of the 2 subjects started with acarbose 100 mg 3x1 converted to DM while the other subject did not, 1 subject started with rosiglitazone 4 mg 1x1, but after withdrawal of the drug continued with pioglitazone 15 mg 1x1, did not convert to DM [9,17], and lastly 1 subject followed without administering any drug therapy converted to DM (continued with metformin 850 mg 2x1 to control glycemia). This female subject had a BMI of 28.3 at baseline and 27.9 at the end of the study and her exercise level was always low.

Discussion

Unhealthy lifestyles and T2DM are tightly linked, with the former being the primary cause of the latter. These lifestyle practices could be attributed to modern industrialized environments at a rate of 80-90% for all cases of T2DM [10] and there is voluminous evidence for the causal link between diet and physical activity and the prevention of T2DM [11,12]. An expanding range of pharmaceutical agents targeting β-cell function or insulin sensitivity have been tested in the prevention of T2DM over the last two decades; these can be broadly grouped as metformin, PPARγ agonists, and α glucosidase inhibitors. In this study there were no statistically significant changes for BMI and exercise levels in the follow-up period, so the rate of prevention achieved might be broadly attributed to drug therapy.

Metformin is a commonly used and well-understood agent all over the world for the prevention of T2DM. In DPP (The Diabetes Prevention Program), metformin was associated with a 31% reduction in the incidence of T2DM at 3 years [6] but a recent meta-analysis demonstrated an average reduction in the risk of T2DM of 40% with metformin [13], which is more comparable to the finding of this study which was 56.4%. Acarbose is another agent which has proved its efficacy and safety in DM therapy and also has been used for prevention. The major study for prevention was STOP-NIDDM (Study to prevent non-insulin dependent diabetes) [7] and the risk reduction rate was 25%.



Graphic 1. Conversion rate.

Table 1. Correlation between conversion rates and various parameters.

		Converted	Unconverted	Total	P
Subjects		17 (43.6 %)	22 (56.4 %)	39 (100 %)	
Gender	Female	12 (40.0 %)	18 (60.0 %)	30 (100 %)	0.327
	Male	5 (55.6 %)	4 (44.4 %)	9 (100 %)	
Education	Illiterate	3 (75.0%)	1 (25.0 %)	4 (100 %)	0.456
	Preliminary	7 (35.0 %)	13 (65.0 %)	20 (100%)	
	Mid	1 (100.0 %)	0 (00.0 %)	1 (100 %)	
	High	5 (45.5 %)	6 (54.5 %)	11 (100 %)	
	College	1 (33.3 %)	2 (66.7 %)	3 (100 %)	
Smoking	Yes	3 (60.0 %)	2 (40.0 %)	5 (100 %)	0.263
	No	8 (33.3 %)	16 (66.7 %)	24 (100 %)	
	Ex Smoker	6 (60.0 %)	4 (40.0 %)	10 (100 %)	
Hypertension	Yes	10 (45.5 %)	12 (54.5 %)	22 (100%)	0.524
	No	7 (41.2 %)	10 (58.8 %)	17 (100 %)	
Dyslipidemia	Yes	16 (45.7 %)	19 (54.3 %)	35 (100 %)	0.407
	No	1 (25.0 %)	3 (75.0 %)	4 (100 %)	

Table 2. Correlation between conversion rates and various parameters.

		Converted	Unconverted	Total	p
Therapy (Baseline)	Metformin 850 1x1	8 (44.4 %)	10 (55.6 %)	18 (100 %)	
	Metformin 850 2x1	5 (55.6 %)	4 (44.4 %)	9 (100 %)	
	No therapy	1 (100 %)	0 (0.0 %)	1 (100 %)	
	Rosiglitazone 4 1x1	0 (0.0 %)	1 (100 %	1 (100 %)	
	Metformin 500 2x1	2 (28.6 %)	5 (71.4 %)	7 (100 %)	
	Acarbose 100 3x1	1 (50.0 %)	1 (50.0 %)	2 (100 %)	0.671
	Metformin 1000 2x1	0 (0.0 %)	1 (100 %)	1 (100 %)	

Table 3. Correlation between BMIs at baseline and last visit.

DM Conversion	BMI Baseline	BMI Last
Mean DM	31.576	30.806
N	17	17
Mean Pre DM	31.727	31.900
N	22	22
Mean Total	31.662	31.423
N	39	39

Although we had only two subjects using acarbose, we found a 50% risk reduction rate.

Thiazolidinedions (TZD) are one of the two agents that have proved their durability in treating DM. We have much data about its efficacy both as monotherapy and in combination with other agents [14,15,16]. Two types of TZDs, rosiglitazone and pioglitazone, have been thoroughly assessed and found to reduce the risk of T2DM by 60-70% over a 2.6- to 3- year period in those with prediabetes [9,17]. However, the impressive efficacy of TZDs in the prevention of T2DM is restricted by serious side effects, which makes their use clinically inappropriate for his group. Trials have shown significant weight gain (2.6-7 kg) compared to placebo. More seriously, TZDs are also associated with an increased risk of cardiovascular disease and other adverse health effects [18]. We had only one subject using TZD and she maintained her status as prediabetes.

Another group of agents that has proved its durability is GLP-1 analogues, which have been used succesfully in the treatment of T2DM. These agents are attractive in prevention of T2DM because they are glucose dependent, meaning their effect on insulin secrection is proportionate to the amount of circulating glucose, thus reducing the risk of hypoglycemia and resulting in significant and sustained weight loss. There is scarcity of studies on this group of agents, but given those unique properties they deserve further investigation as DM prevention therapies and they might be the first line of therapy in DM prevention in the future. For example, just 20 weeks of liraglutide therapy has been shown to be effective and reduced the prevalence of prediabetes by 84-96% depending on the dosage used [19].

Nevertheless, although national organizations and regulatory authorities are increasingly recommending the use of metformin, with the other agents likely to be recommended in the future, there remains some controversy around the use of pharmaceutical intervention, and lifestyle modification programs should be the focus of diabetes prevention initiatives. In our daily practice, if we encounter a subject with a prediabetic state with fasting blood glucose over 110 or A1c over 6%, we additionally request an insulin level and C-peptide level. Sometimes an OGTT is performed to obtain 2-hour glucose level. However, there are important practical limitations regarding the utility and clinical value of carrying out OGTTs to identify those with a high risk of T2DM in routine care.Therefore, instead of performing an OGTT, we perform, in addition to blood tests, a risk analysis using variables such as sex,age,ethnicity, BMI, family history of T2DM, cardiovascular diseases, and hypertension assessments for treatment decisions. After taking into considiration all these factors, we decide whether therapy will involve a lifestyle modification program, pharmaceutical intervention, or both. Because for most healthcare units, these tools might be overwhelming or impossible, risk assessment tools such as FINDRISC [20], which is developed for identification of those with a high risk of T2DM, might be preferred.

In conclusion, one of the most confusing questions for physicians serving their patients with DM, a complicated and multifaceted disease, is to decide whether to apply pharmaceutical intervention in the face of prediabetes. That decision means the patients will have to use the drug for their entire life, and we know that some prediabetics do not convert to overt DM untill near the end of their lives. On the other hand, we know the devastating effects of DM and DM-associated diseases. So, preventing or delaying DM in any way is a great benefit to the patients.

At the end of this study we found a 43.6% conversion rate to overt T2DM. Thus, this small-scale but long-term study indicates the possibility that DM can be at least partly prevented or delayed for years through pharmaceutical intervention. Even if the prediabetic state converts to DM, it can be managed with little intervention, achieving nearly the same glucose levels compared to prediabetes.

Nonetheless, as mentioned earlier it should be kept in mind that the lifestyle practices are the first-line alternatives and the mainstay of prevention intervention programs for diabetes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Bansal N: Prediabetes diagnosis and treatment: A review. World J Dia. 2015;6(2):296-303.
2. Buysschaert M, Medina JL, Buysschaert B, Bergman M: Definitions (and current controversies) of diabetes and prediabetes. Curr Dia Rev. 2016;12(1):8-13.
3. Tabak G, Herder C, Rathmann W, Brunner E, Kwimaki M. Prediabetes : a high-risk state for diabetes development. Lancet 2012;379(9833):2279-90.
4. Mostafa SA, Khunti K, Srinivasan BT, Webb D, Grey LJ, Davies MJ: The potential impact and optimal cut-points of using glycated haemaglobin, HbA1c,to detect people with impaired glucose regulation in a UK multi-ethnic cohort. Diabetes Res Clin Pract. 2010;90(1):100-8
5. James C, Bullard KM, Rolka DB, Geiss LS, Williams DE, Covie CC, et al.: Implications of alternative definitions of prediabetes for prevalence in US, adults. Diabetes Care 2011;34(2):387-91.
6. Knowler WC, Barrett-Connor E, Fowler SE: the Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with life style intervention or metformin. N Engl J Med. 2002;346(6):393-403.
7. Oja P, Titze S: Physical activity recommendations for puplic health: development and policy context. EPMA J. 2011;2(3):253-9.
8. Chiasson JL: Acarbose for the prevention of diabetes, hypertension, and cardiovascular disease in subjects with impaired glucose tolerance: the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) Trial. Endocr Pract. 2006;12:25-30.
9. DeFronzo RA, Devjit Tripathy, Dawn C, MaryAnn B, George B, Thomas B, et al.: Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. N Engl J Med 2011; 364:1104-15.
10. Mozaffarian D, Kamineni A, Carnethon M, Djousse L, Mukamal KJ, Siscovick D: Lifestyle risk factors and new onset diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med 2009;169(8):798-807.
11. Hawley JA: Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev. 2004;20(5):383-93.
12. Telford RD: Low physicial activity and obesity: causes of chronic disease or simply predictors? Med Sci Sports Exerc. 2007;39(8):1233-40
13. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE: Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med. 2008;121(2):149-57.
14. Aranoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL: Pioglitazone hydrocholoride monotherapy improves glycemic control in the treat-

ment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000 Nov;23(11):1605-11.
15. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE: Pİogitazon 026 Study Group. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis. 2001;12(5):413-23.
16. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL: Pioglitazone hydrocholoride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, plecebo-controlled study. The Pioglitazone 027 Study Group. Clinical Therapeutics. 2000;22(12):1395-409.
17. Gerstein HC, Yusuf S, Bosch J, Pouge J, Sheridan P, Dinccag N, at al.: DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368(9549):1096-1105.
18. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl JMedicine. 2007;356:2457-71
19. Astrup A, Rosner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al.: Effects of Liraglutide in the treatment of obesity: a randomised double-blind, placebo controlled study. Lancet 2009;374(9701):1606-16.
20. Lindström J, Tuomilehto J: The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care. 2003;26(3):725-31.

How to cite this article:
Eker S. Conversion rate of prediabetes to diabetes in long-term followed patients. Ann Clin Anal Med 2019;10(4): 421-5.